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TRANSMITTAL FORM

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First Named Inventor	Gary S. Grubb
Art Unit	1617
Examiner Name	San Ming R. Hui
Attorney Docket Number	WYTH0106-100 (AM100058)

ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
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- ☐ Drawing(s)
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- ☐ Petition to Convert to a Provisional Application
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- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below)*:
  - Appellant's Reply Brief Pursuant to 37 C.F.R. § 41.41 dated September 21, 2006 (in triplicate)

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Date	September 21, 2006	Reg. No.	42,982

CERTIFICATE OF TRANSMISSION/MAILING

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Signature	Michael A Patané		
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Gary S. Grubb	**Art Unit:**	1617
		Examiner:	San Ming R Hui
Serial No.:	09/872,250	**Confirmation No.:**	4735
Filed:	June 1, 2001	**Docket No.:**	WYTH0106-100 (AM100058)

For: STARTER KIT FOR LOW DOSE ORAL CONTRACEPTIVES

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APPELLANT'S REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

I. Summary of the Argument on Reply

The Office has not demonstrated a proper motivation to combine the base references, Endrikat et al. and Hogden. Although the problem of increased breakthrough bleeding in initial cycles was recognized in the art, breakthrough bleeding rates were successfully reduced to acceptable levels, even in the low dose regimens. Each of the references teaches only that relatively low doses of estrogen (20mcg) meet the goal of reducing overall estrogen intake while balancing the desire for reduced intermenstrual bleeding in the form of spotting or breakthrough bleeding. One skilled in the art reading either Endrikat et al. and Hogden, alone and in combination, simply would not have the desire to modify the references to administer relatively high initial doses (30 mcg) followed by relatively low doses (20mcg) of estrogen. Endrikat et al. teaches that the lower dose regimen should be the first line treatment, with the higher dose being administered when the patient does not respond to the lower dose. Hogden teaches that the lower dose reduces the overall estrogen intake while having intermenstrual bleeding rates similar to other oral contraceptives.

Endrikat et al. recognizes increased breakthrough bleeding in the initial cycle(s) is due to adaptation of the endometrium as pointed out in the Examiner's Answer. Endrikat et al. recognizes this is the case with both the 30 mcg and 20 mcg doses. Both Endrikat and Hogden,

recognizing this, conclude only that initial cycle(s) will be plagued with higher breakthrough bleeding rates compared to subsequent cycles, regardless of dose. Therefore, Endrikat and Hogden are concerned, NOT with reducing breakthrough bleeding in initial cycles to levels similar to later cycles, but rather Edrikat and Hogden are directed to providing effective overall control with the lowest possible dose. Each seems to expect and accept higher breakthrough bleeding rates in initial cycle(s), consistent with the thinking of those of skill in the art at the time.

With the benefit of hindsight and Appellants' disclosure, one can now look at the data in Endrikat containing a side by side comparison and see, as directed by Appellants, the benefits of a hybrid dosing regimen including initial higher dosages followed by subsequent lower dosages to achieve roughly similar breakthrough bleeding rates throughout the entire treatment period. At the time, however, not even the authors suggested such a hybrid dosing regime. Endrikat teaches to begin all treatments with as low a dose as possible, moving to higher dose treatment only if the low-dose is unacceptable or not tolerated. (Thus, teaching move from low dose to high dose in direct contraction to Appellants' claims.) The focus of both Endrikat and Hogden is to lower overall estrogen intake while maintaining acceptable levels of breakthrough bleeding, not to reduce breakthrough bleeding in initial cycles.

Only Appellants have suggested an approach taking the best of the high-dose and low-dose treatments. Only Appellants thought the initial breakthrough bleeding rates of the low-dose treatment needed to be addressed. Only Appellants felt an initially high dose and all its potential risks and drawbacks was worthwhile to achieve lower initial breakthrough rates given the overall reduction in estrogen intake. Until now, the thinking in the art in balancing initial breakthrough vs. potential risk associated with higher initial doses, tipped in favor of higher initial breakthrough. Appellants, for the first time, teach a hybrid approach, favoring low breakthrough bleeding rates over reduced risks for initial doses, and favoring low dose in subsequent cycles which benefit from acceptable rates and reduced risk. Thus, Appellants have taken an overall approach whereby the hybrid regimen benefits overall from reduced estrogen intake but also benefits from reduced breakthrough bleeding, even in initial cycles.

The art of record simply does not, absent Appellants' own teachings, provide any motivation or suggestion to achieve a hybrid dosing regimen or a multicycle kit for facilitating such a regimen. Accordingly, the obviousness rejection under 35 U.S.C. § 103(a) should be withdrawn.

II. Grounds of Rejection

The Examiner's Answer (Answer) indicates that it would have been obvious to combine the oral contraceptives packs of 30mcg and 20 mcg of Ethinyl estradiol together in a kit, and to employ various progestins therein.

Motivation for such a combination is alleged to result from Hogden's method of reducing breakthrough bleeding and it's sole drawback of breakthrough bleeding in the first cycle. The Answer indicates one in possession of the teachings of Endrikat et al. "would reasonably expect to employ a regimen comprising a dose of 30 mcg of ethinylestradiol in the first cycle in the Hogden's method in order to let the endometrium adapt to the exogenous hormones as well as reduce the breakthrough bleeding in the first cycle and thereby improving Hogden's method."

The Answer also alleges it would be obvious to employ the various progestins as claimed, since selecting obvious alternatives among known progestins would allegedly be obvious.

Appellant's reply brief will focus on the combination of the Endrikat et al. and Hogden methods, since failure to motivate this basic combination is dispositive on the issue of obviousness.

III. Response To Issues Raised By The Examiner

The rejection under 35 U.S.C. § 103 (a) of claims 1-11 as obvious over Endrikat et al. Hogden et al. (U.S. Patent No. 5,552,394) and Katzung, and over Endrikat et al. in view of Katzung were maintained.

A. The Office Has Failed To Provide Motivation To Combine

Despite the Answer's characterization, there is no motivation to combine the teachings of Endrikat et al. and Hogden. The Answer focuses on the alleged fact that Hogden has one drawback – failure to reduce the breakthrough bleeding in the initial cycle and the fact that Endrikat's higher doses, benefit from reduced breakthrough levels when compared to Hogden's low dose regimen, even in initial cycles. The Answer alleges that those of skill in the art would have realized the drawback of the Hogden regimen and "would have been motivated to improve

the contraceptive regimen for reducing side effects by increasing the initial dosage of estrogen and then subsequently reducing the dose." (See Answer, page 5.)

Appellants respectfully disagree. One skilled in the art reading Endrikat or Hogden, alone or combined, are taught only that breakthrough bleeding is acceptable at higher levels in initial cycles and that such incidence can be reduced in subsequent cycles. The overall teaching of both Endrikat and Hogden is that some level of breakthrough bleeding is acceptable and must be balanced against the other benefits of a low-dose administration. Those of skill in the art were concerned, not with reducing breakthrough bleeding in initial cycles, but rather with reducing estrogen administration *overall* while maintaining acceptable breakthrough rates. In Hogden, this was done, not through increasing estrogen levels in each dose, but rather by administering more doses per cycle at a lower dosage. In Endrikat, acceptable breakthrough rates were achieved with a 20mcg dose and therefore, the 20 mcg dose is the preferred starting dose, to be increased only if the patient is not satisfied.

There is simply no evidence of record that indicates that those of skill in the art were not happy with the balance of breakthrough bleeding vs. benefit of reduced overall estrogen administration, and therefore interested in reducing breakthrough in the initial cycles. Such a suggestion is only found in Appellants' specification.

The Office is suggesting a motivation to combine the references where one simply does not exist. Endrikat et al. shows both a 20mcg treatment regimen and a 30 mcg regimen, in a side-by-side comparison. Given the benefit of Appellant's teachings, one may determine from the comparison, that a combined treatment could be desirable. Endrikat et al., however, concludes in full view of the data, not that a combined treatment would be most beneficial, but rather the 20mcg treatment should be used as the first line of treatment – even in light of comparatively greater incidence of breakthrough bleeding in the initial cycles. Endrikat et al. reflects the thinking of those of skill in the art – higher levels of breakthrough bleeding are acceptable in favor of reduced overall estrogen intake.

Thus, the only evidence of a motivation or suggestion for a combined administration is found in Appellants' own specification, not in the cited art.

B. The References Fail To Teach The Alteration Of Dosage Of Estrogen In Different Cycles

As alluded to above, each of Endrikat et al. and Hogden teach administration of ethinylestradiol according to several treatment regimes. Common to both Endrikat and Hogden is that from cycle to cycle, the administration is identical. It should be noted that it is common in contraceptive administration for the dosage and/or content to differ on different days within a cycle. Altering dosages from one cycle to the next as part of a planned treatment regimen is not so commonplace. Appellants have claimed a cycle pack for implementing such a multi-cycle treatment regime. Neither Endrikat nor Hogden teach altered doses from one cycle to the next, and thus do not teach or suggest the need for a multi-cycle pack. Altering doses from one cycle to the next creates greater compliance issues, requires additional packaging, and creates other concerns.

The Answer indicates the rejection is not based on the altering of the estrogen dosage, but rather that the prior art provides "the motivation to improve the Hogden's method by employing a higher dosage initially to avoid breakthrough bleeding." As discussed above, however, there is nothing in either Endrikat or Hogden that suggests improving the Hogden method by increasing initial dosages. The focus of both references is to reduce overall estrogen dosages. The only way to combine the references to arrive at Appellants' claimed invention is to alter estrogen dosages from initial cycles to later cycles – which simply is not taught or suggested by either Endrikat or Hogden. Thus, the cited references do not provide a motivation or suggestion to reach the combination of Appellants' claims.

C. The references do not recognize any benefit of increased initial estrogen doses.

The Answer dismisses Appellants' argument that Endrikat and Hogden are silent with respect to initial high doses of estrogen as unconvincing. The Answer again indicates those of skill in the art would reasonably expect to employ the 30 mcg dose of Endrikat in the first cycle of Hogden's method to let the endometrium adapt to the exogenous hormones and reduce the breakthrough bleeding. Neither Endrikat nor Hogden teach or suggest that the increased breakthrough bleeding rates of initial cycles need to be addressed. In fact, Endrikat indicates that "in relation to all cycles, intermenstrual bleeding rates were remarkably lower" (See Abstract; emphasis added.) Endrikat teaches in the Abstract, " A higher incidence of intermenstrual bleeding was apparent under the 20mcg EE2 oral contraceptive. . . .However,

the incidence was within a range that corresponds to that of other OCs." Thus, Endrikat teaches only that 20 mcg EE2 treatment regimes are acceptable and have intermenstrual bleeding rates similar to acceptable oral contraceptives. One skilled in the art would not be motivated to raise overall estrogen dosage by administering greater levels of estrogen in the initial cycles, since reduced estrogen content is the goal, and bleeding rates are acceptable with the lower level of estrogen. Similarly, Hogden appears to be satisfied with the bleeding rates, especially in light of the reduced overall estrogen intake.

Thus, Appellants respectfully assert that the references are silent with respect to any benefit of an initial higher estrogen content dosage, and would seem to disfavor such an increased dose, since the bleeding rates are acceptable and overall estrogen intake is reduced.

D. The cited references are silent with respect to the problem of breakthrough bleeding in initial cycles.

The Answer dismisses Appellants' arguments as unconvincing and merely reiterates its position that Hogden's only drawback, breakthrough in the initial cycle, could be remedied by administering the higher doses found in Endrikat. Appellants assert that one skilled in the art would not be motivated to use the higher doses of Endrikat in the method of Hogden because both references are silent with respect to addressing the perceived problem of breakthrough bleeding in initial cycles. Furthermore, those of skill in the art would not be motivated to make such a change because Endrikat, itself, indicates that the lower dose treatment should be used, even despite higher levels of breakthrough bleeding in the initial cycles.

The Answer seems to making the point that one skilled in the art would have been motivated "to let the endometrium adapt to the exogenous hormones as well as reduce the breakthrough bleeding in the first cycle." However, this adaptation period is required in both the 20 mcg regimen and the 30 mcg regimen, there is simply nothing in either reference to suggest beginning with the 30mcg treatment and moving to a 20mcg treatment and certainly no suggestion of a multi-cycle kit or pack for facilitating such administration. The only such teaching is found in Appellants' disclosure.

E. Appellants' claimed multi-cycle kit and treatment regimen are unconventional.

The Answer indicates that Appellants argument that the hybrid administration of 30 mcg in initial cycles followed by 20 mcg in subsequent cycles is not unconventional to the teachings

of the prior art. The Answer further notes Endrikat does not discourage the use of a relatively high dose of estrogen in the initial phase. Appellants note that Endrikat also does not teach, suggest, or even hint the dosage should vary in initial phases, except to say that where initial low doses are not effective or tolerable, the dose can be raised to the higher dose. Neither Endrikat nor Hogden suggest varying dose from high dose to low dose as described by Appellants. Accordingly, neither Endrikat or Hogden, alone or in combination, teach or suggest the multi-cycle pack claimed by Appellants. Appellants' claimed cycle pack and the treatment regimen it facilitates is unconventional from the cited art in that it facilitates administration of varying levels of estrogen from one cycle to the next, to allow higher estrogen administration in initial cycles. This simply is not taught or suggested by the cited references.

F. The rejection is based on impermissible hindsight, using Appellants' disclosure as a blue print.

The Answer notes that an obviousness determination is proper if it "does not include knowledge gleaned only from the applicant's disclosure." (citation omitted.) Here, the only teaching of a multi-cycle treatment regimen with higher initial estrogen doses followed by lower subsequent doses is Appellants' disclosure. The only disclosure of a multi-cycle pack to facilitate administration of such a treatment regimen is Appellants' disclosure. Neither Endrikat nor Hogden teach such a hybrid treatment regimen or a multi-cycle pack as claimed. As noted above, not even the Endrikat authors recognized the possibility of a hybrid method even when looking at a side-by-side comparison of the 20 mcg and 30 mcg treatments. Rahter, since bleeding patterns were acceptable in both regimens, the lower dose regimen is favored by Endrikat. There is no additional art cited to make the link from the separate treatment regimens taught by Endrikat and the hybrid treatment regimen taught by Appellants. Only by using Appellants disclosure does one find the motivation to employ a hybrid treatment regimen. Accordingly, the rejection is based upon impermissible hindsight.

G. Despite the long-felt need, only Appellants recognized and addressed the continued need to reduce initial breakthrough bleeding rates.

The Answer indicates that Appellants' argument concerning long-felt need is not convincing since there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. Appellants assert that the lack of such evidence supports our contentions above. Those of skill in the art, although recognizing the problem of increased

breakthrough bleeding in initial cycles, were satisfied with the rates and considered them acceptable. That is, until Appellants addressed the problem head on.

The Answer also indicates there is no evidence that if persons skilled in the art were working on the problem that they would be unable to solve the problem given the teachings of the cited references. However, there is no evidence of record to show that those of skill in the art were unsatisfied with the initial breakthrough bleeding rates of Endrikat or Hogden, and thus would have any desire to address them. Indeed, Endrikat and Hogden both indicate the breakthrough bleeding rates are acceptable and, thus, favor the low-dose treatment regimens.

Only Appellants **both** recognized **and** addressed the problem of increased breakthrough bleeding in initial cycles. Although the problem of higher breakthrough bleeding rates in initial cycles had been recognized previously, the rates in Edrikat and Hogden were considered acceptable, and therefore further reduction was not required or desired. Thus, those of skill in the art would not have been motivated to further address the problem.

Conclusion

Appellants respectfully assert that independent claim 1 and all claims dependent therefrom are patentable over the cited combination of references. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fee or underpayment thereof or credit any overpayment to deposit account no. 50-1275.

Early and favorable action by the Board is respectfully requested.

Respectfully submitted,

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